PT. PFIZER INDONESIA
Local Product Document

Generic Name: Olmesartan medoxomil, Hydrochlorothiazide
Trade Name: **OLMETEC PLUS**
CDS Effective Date: June, 2020
Supersedes: May, 2016

1. NAME OF THE MEDICINAL PRODUCT
Olmetec Plus 20/12.5 mg
Olmetec Plus 40/12.5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Olmetec Plus 20/12.5 mg tablet contains 20 mg olmesartan medoxomil and 12.5 mg hydrochlorothiazide

Each Olmetec Plus 40/12.5 mg tablet contains 40 mg olmesartan medoxomil and 12.5 mg hydrochlorothiazide

For excipients, see section 6.1 - **List of excipients**.

3. PHARMACEUTICAL FORM
Film-coated tablet.

Olmetec Plus 20/12.5 mg tablet: Reddish-yellow, round, film-coated tablet with C22 debossed on one side.

Olmetec Plus 40/12.5 mg tablet: Reddish-yellow, oval, film-coated tablet with C23 debossed on one side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension.

Olmetec Plus fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on olmesartan medoxomil or hydrochlorothiazide alone.

4.2 Posology and method of administration
Adults
Olmetec Plus is administered once daily, with or without food, in patients whose blood pressure is not adequately controlled by olmesartan medoxomil or hydrochlorothiazide alone.

When clinically appropriate, direct change from monotherapy to the fixed combination may be considered. Dose titration of the individual components is recommended:

Olmetec Plus 20/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with hydrochlorothiazide 12.5 or 25 mg monotherapy, or Olmetec 20 mg alone. If additional blood pressure lowering is required, the dose of each monocomponent may be titrated to the strength of Olmetec Plus 40/12.5 mg and subsequently, if required to 40/25 mg.

Olmetec Plus 40/12.5 mg and Olmetec Plus 40/25 mg may be administered in patients whose blood pressure is not adequately controlled by Olmetec 40 mg alone, hydrochlorothiazide alone, or Olmetec Plus 20/12.5 mg.

Elderly
No initial dosage adjustments recommended for elderly patients (see section 5.2 - **Pharmacokinetic properties**).

Renal impairment
In patients with mild to moderate renal impairment (creatinine clearance of 30 – 60 mL/min) the dosage of olmesartan medoxomil should not exceed 20 mg daily (i.e., Olmetec Plus 20/12.5 mg), owing to limited experience of higher dosages of Olmetec in this patient group (see section 5.2 - **Pharmacokinetic properties**). When Olmetec Plus is used in such patients, periodic monitoring of renal function is advised (see section 4.4 - **Special warnings and special precautions for use**). Olmetec Plus is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) (see section 4.3 - **Contraindications**).

Hepatic impairment
The use of Olmetec Plus in patients with hepatic impairment is not recommended since there is currently limited experience of olmesartan medoxomil in this patient group (see sections 4.4 - **Special warnings and special precautions for use** and 5.2 - **Pharmacokinetic properties**).

Children and adolescents
The safety and efficacy of Olmetec Plus have not been established in children and adolescents up to 18 years of age.

4.3 Contraindications
Pregnancy (see section 4.6 - **Pregnancy and lactation**).

Lactation (see section 4.6 - **Pregnancy and lactation**).

Hypersensitivity to the active substances, to any of the excipients (see section 6.1 - **List of excipients**) or to other sulphonamide-derived substances (since hydrochlorothiazide is a sulphonamide-derived medicinal product).

Severe renal impairment (creatinine clearance <30 mL/min).

Refractory hypokalaemia, hypercalcaemia and symptomatic hyperuricaemia.

Cholestasis and biliary obstructive disorders.

Do not co-administer aliskiren with olmesartan medoxomil-hydrochlorothiazide in patients with diabetes (see section 4.5 - **Interaction with other medicinal products and other forms of interaction**).

4.4 Special warnings and special precautions for use
Pregnancy and lactation:
See section 4.6 - **Pregnancy and lactation** regarding use in pregnancy and lactation.

Intravascular volume depletion:
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Olmetec Plus.

Other conditions with stimulation of the renin-angiotensin-aldosterone system:
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure.

Renovascular hypertension:
There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation:
Olmetec Plus should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min) (see section 4.3 - **Contraindications**). No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance is 30 mL/min, <60 mL/min). However, in such patients Olmetec Plus should be administered with caution and periodic monitoring of serum potassium, creatinine and uric acid levels is recommended. Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function. There is no experience of the administration of Olmetec Plus in patients with a recent kidney transplantation.

Acute myopia and secondary angle-closure glaucoma:
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Sprue-like enteropathy:
Severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan medoxomil months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan medoxomil, exclude other etiologies. Consider discontinuation of olmesartan medoxomil-hydrochlorothiazide in cases where no other etiology is identified.

Hepatic impairment:
There is currently limited experience of olmesartan medoxomil in patients with mild to moderate hepatic impairment and no experience in patients with severe hepatic impairment. Furthermore, minor alterations of fluid and electrolyte balance during thiazide therapy may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease. Therefore, use of Olmetec Plus in patients with hepatic impairment is not recommended (see section 4.2 - **Posology and method of administration**). Use of olmesartan medoxomil in patients with biliary obstruction is contraindicated (see sections 4.3 - **Contraindications** and 5.2 - **Pharmacokinetic properties**).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism:
Patients with primary aldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Olmetec Plus is not recommended in such patients.

Metabolic and endocrine effects:
Thiazide therapy may impair glucose tolerance. In diabetic patients, dosage adjustments of insulin or oral hypoglycaemic agents may be required (see section 4.5 - **Interaction with other medicinal products and other forms of interaction**). Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Hyperuricaemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy.

Electrolyte imbalance:
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances, such as nausea or vomiting (see section 4.8 - **Undesirable effects**).

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with olmesartan medoxomil may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH. Conversely, due to antagonism at the angiotensin-II receptors (AT'1) through the olmesartan medoxomil component of Olmetec Plus hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes should be co-administered cautiously with Olmetec Plus (see section 4.5 - **Interaction with other medicinal products and other forms of interaction**).

Olmetec Plus also contains olmesartan, a drug that inhibits the renin-angiotensin system (RAS). Drugs that inhibit the RAS can cause hyperkalaemia. Monitor serum electrolytes periodically.

There is no evidence that olmesartan medoxomil would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Lithium:
As with other medicinal products containing angiotensin II receptor antagonists and thiazide in combination, the co-administration of Olmetec Plus and lithium is not recommended (see section 4.5 - **Interaction with other medicinal products and other forms of interaction**).

Other:
As with any anti-hypertensive agent, excessive blood pressure decrease in patients with ischaemic heart disease or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

Pediatric use
Safety and effectiveness in pediatric patients have not been established.

Geriatric use
Clinical studies of olmesartan medoxomil and hydrochlorothiazide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

Olmesartan and hydrochlorothiazide are substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

4.5 Interaction with other medicinal products and other forms of interaction
Effects of other medicinal products on Olmetec Plus:
Dual Blockade of the Renin-Angiotensin System (RAS)
Dual blockade of the RAS with angiotensin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors or aliskiren is associated with increased risks of hypotension, hyperkalemia and changes in renal function (including acute renal failure) compared to monotherapy. Monitor blood pressure, renal function and electrolytes in patients on olmesartan and other agents that affect the RAS.

Use with aliskiren:
Do not co-administer aliskiren with olmesartan medoxomil in patients with diabetes (see section 4.3 - **Contraindications**) because dual use is associated with increased risks of

hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

Non-steroidal anti-inflammatory drugs (NSAIDs):
NSAIDs and ARBs may act synergistically by decreasing glomerular filtration. The concomitant use of NSAIDs and ARBs may increase the risk of worsening renal function. Monitoring of renal function at the beginning of treatment should be recommended as well as regular hydration of the patient.

Additionally, concomitant treatment can reduce the antihypertensive effect of ARBs, leading to their partial loss of efficacy.

Use with Colesevelam Hydrochloride:
Concurrent administration of bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan. Administration of olmesartan at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect (see section 5 - **PHARMACOLOGICAL PROPERTIES**).

Drug interaction with bile acid sequestering agent colesevelam:
Concomitant administration of 40 mg olmesartan medoxomil and 3,750 mg colesevelam hydrochloride in healthy subjects resulted in 28% reduction in C_{max} and 39% reduction in AUC of olmesartan. Lesser effects, 4% and 15% reduction in C_{max} and AUC, respectively, were observed when olmesartan medoxomil was administered 4 hours prior to colesevelam hydrochloride.

Medicinal products affecting potassium levels:
The potassium-depleting effect of hydrochlorothiazide (see section 4.4 - **Special warnings and special precautions for use**) may be potentiated by the co-administration of other medicinal products associated with potassium loss and hypokalaemia (e.g., other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium or salicylic acid derivatives).

Conversely, based on experience with the use of other drugs that affect the renin angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (e.g., heparin) may lead to increases in serum potassium (see section 4.4 - **Special warnings and special precautions for use**).

If drugs which affect potassium levels are to be prescribed in combination with Olmetec Plus, monitoring of potassium plasma levels is advised.

Other antihypertensive agents:
The blood pressure lowering effect of Olmetec Plus can be increased by concomitant use of other antihypertensive medications.

Non-steroidal anti-inflammatory drugs:
The administration of a non-steroidal anti-inflammatory drug may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients. In elderly patients and patients who may be dehydrated, there is a risk of acute renal failure, therefore monitoring of renal function at the initiation of treatment is recommended.

Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Baclofen, amifostine:
Potentiation of antihypertensive effect may occur.

Cholestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

Anticholinergic agents (e.g., atropine, biperiden):
Increase of the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Effects of Olmetec Plus on other medicinal products:
Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and, rarely, with angiotensin II antagonists. In addition, renal clearance of lithium is reduced by thiazides, and consequently the risk of lithium toxicity may be increased. Therefore, use of Olmetec Plus and lithium in combination is not recommended (see section 4.4 - **Special warnings and special precautions for use**). If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Medicinal products affected by serum potassium disturbances:
Periodic monitoring of serum potassium and ECG is recommended when Olmetec Plus is administered with drugs affected by serum potassium disturbances (e.g., digitalis glycosides and antiarrhythmics) and with the following torsades de pointes-inducing medicinal products, hypokalaemia being a predisposing factor to torsades de pointes:
- Class Ia antiarrhythmics (e.g., quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (e.g., amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (e.g., thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e.g., bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, terfenadine, vincamine IV).

Digitalis glycosides:
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Antidiabetic drugs (oral agents and insulin):
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug may be required (see section 4.4 - **Special warnings and special precautions for use**).

Metformin:
Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Beta-blockers and diazoxide:
The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Pressor amines (e.g., noradrenaline):
The effect of pressor amines may be decreased.

Non-depolarizing skeletal muscle relaxants (e.g., tubocurarine):
The effect of non-depolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol):
Dosage adjustment of uricosuric medications may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Calcium salts:
Thiazide diuretics may increase serum calcium levels due to decreased excretion (see section 4.4 - **Special warnings and special precautions for use**). If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Amantadine:
Thiazides may increase the risk of adverse effects caused by amantadine.

Cytotoxic agents (e.g., cyclophosphamide, methotrexate):
Thiazides may reduce the renal excretion of cytotoxic drugs and potentiate their myelosuppressive effects.

Additional information:
Concomitant administration of olmesartan medoxomil and hydrochlorothiazide had no clinically-relevant effects on the pharmacokinetics of either component in healthy subjects.

After treatment with antacid (aluminum magnesium hydroxide), a modest reduction in bioavailability of olmesartan was observed. Olmesartan medoxomil had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin.

Co-administration of olmesartan medoxomil with pravastatin had no clinically relevant effects on the pharmacokinetics of either component in healthy subjects.

Olmesartan had no clinically relevant inhibitory effects on human cytochrome P450 enzymes 1A1/2, 2A6, 2C8/9, 2C19, 2D6, 2E1 and 3A4 *in vitro*, and had no or minimal inducing effects on rat cytochrome P450 activities. No clinically relevant interactions between olmesartan and drugs metabolised by the above cytochrome P450 enzymes are expected.

4.6 Pregnancy and lactation
Use in pregnancy (see section 4.3 - Contraindications):
There is no experience with the use of Olmetec Plus in pregnant women. Studies in mice and rats using olmesartan medoxomil/hydrochlorothiazide combinations do not indicate a teratogenic effect, but foetotoxicity has been shown in rats. Thiazides cross the placental barrier and appear in cord blood. They may cause foetal electrolyte disturbances and possible other reactions that have occurred in adults. Cases of neonatal thrombocytopenia or foetal or neonatal jaundice have been reported with maternal thiazide therapy.

If pregnancy occurs during therapy, Olmetec Plus must be discontinued as soon as possible.

Olmetec Plus is contraindicated during pregnancy. If the patient becomes pregnant while taking Olmetec Plus, the patient should be apprised of the potential hazard to a fetus. Should exposure to Olmetec Plus have occurred from the second trimester forward, ultrasound examinations of the renal function and of the skull are recommended. Newborns exposed to angiotensin II antagonists in utero must be closely monitored for the occurrence of hypotension, oliguria, and hyperkalaemia.

Use during lactation (see section 4.3 - Contraindications):
Olmesartan is excreted in the milk of lactating rats but it is not known whether olmesartan is excreted in human milk. Thiazides appear in human milk and may inhibit lactation. Mothers must not breast-feed if they are taking Olmetec Plus.

4.7 Effects on ability to drive and use machines
The effect of Olmetec Plus on the ability to drive and use machines has not been specifically studied. However, it should be borne in mind that dizziness or fatigue may occasionally occur in patients taking antihypertensive therapy.

4.8 Undesirable effects

Fixed-dose combination:

In clinical trials involving 2341 patients treated with olmesartan medoxomil/hydrochlorothiazide combinations and 466 patients treated with placebo for periods of up to 21 months, the overall frequency of adverse events on olmesartan medoxomil/hydrochlorothiazide combination therapy was similar to that on placebo.

Discontinuations due to adverse events were also similar for olmesartan medoxomil/hydrochlorothiazide (2%) and placebo (3%). The frequency of adverse events on olmesartan medoxomil/hydrochlorothiazide relative to placebo appeared to be unrelated to age (<65 years versus ≥65 years), gender or race.

The only adverse event which was statistically significantly more frequent on olmesartan medoxomil/hydrochlorothiazide than on placebo was dizziness (3% versus 1%). The incidence of dizziness was not dose related.

Adverse Events of potential clinical relevance are listed below by System Organ Class. Frequencies are defined as: common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000).

Metabolism and nutrition disorders:
Uncommon: Hyperuricaemia, hypertriglyceridaemia.

Nervous system disorders:
Common: Dizziness.
Uncommon: Syncope.

Cardiac disorders:
Uncommon: Palpitations.

Vascular disorders:
Uncommon: Hypotension, orthostatic hypotension.

Skin and subcutaneous tissue disorders:
Uncommon: Rash, eczema.

General disorders:
Uncommon: Weakness.

Investigations:
Uncommon: Blood potassium decreased, blood potassium increased, blood urea increased.

Laboratory findings
In clinical trials, clinically important changes in standard laboratory parameters were rarely associated with olmesartan medoxomil/hydrochlorothiazide.

Minor increases in mean uric acid, blood urea nitrogen and creatinine values and minor decreases in mean haemoglobin and haematocrit values were observed during treatment with olmesartan medoxomil/hydrochlorothiazide.

Additional information on individual components:
Undesirable effects previously reported with either of the individual components may be potential undesirable effects with Olmetec Plus, even if not observed in clinical trials with this product.

Olmesartan medoxomil
Market experience
The following adverse reactions have been reported in post-marketing experience. They are listed by System Organ Class and ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000) including isolated reports:

System Organ Class	Very Rare
Blood and lymphatic system disorders	Thrombocytopenia
Nervous system disorders	Dizziness, headache
Respiratory, thoracic and mediastinal disorders	Cough
Gastrointestinal disorders	Abdominal pain, nausea, vomiting diarrhea, sprue-like enteropathy
Skin and subcutaneous tissue disorders	Pruritus, exanthem, rash, allergic conditions such as angioneurotic oedema, dermatitis allergic, face oedema and urticaria, anaphylactic reaction
Musculoskeletal and connective tissue disorders	Muscle cramp, myalgia
Renal and urinary disorders	Acute renal failure and renal insufficiency (See also under Investigations)
General disorders and administration site conditions	Asthenic conditions such as asthenia, fatigue, lethargy, malaise, peripheral oedema
Investigations	Abnormal renal function tests such as blood creatinine increased and blood urea increased, increased hepatic enzymes
Metabolic and nutritional disorders	Hyperkalaemia

Clinical trials
In double-blind, placebo-controlled monotherapy studies, the overall incidence of treatment-emergent adverse events was 42.4% on olmesartan medoxomil and 40.9% on placebo.

In placebo-controlled monotherapy studies, the only adverse drug reaction that was unequivocally related to treatment was dizziness (2.5% incidence on olmesartan medoxomil and 0.9% on placebo).

In long-term (2-year) treatment, the incidence of withdrawals due to adverse events on olmesartan medoxomil 10 - 20 mg once daily was 3.7%.

The following adverse events have been reported across all clinical trials with olmesartan medoxomil (including trials with active as well as placebo control), irrespective of causality or incidence relative to placebo. They are listed by body system and ranked under headings of frequency using the conventions described above:

Central nervous system disorders:
Common: Dizziness.
Uncommon: Vertigo.

Cardiovascular disorders:
Rare: Hypotension.
Uncommon: Angina pectoris.

Respiratory system disorders:
Common: Bronchitis, cough, pharyngitis, rhinitis.

Gastrointestinal disorders:
Common: Abdominal pain, diarrhoea, dyspepsia, gastroenteritis, nausea.

Skin and appendages disorders:
Uncommon: Rash.

Musculoskeletal disorders:
Common: Arthritis, back pain, skeletal pain.

Urinary system disorders:
Common: Haematuria, urinary tract infection.

General disorders:
Common: Chest pain, fatigue, influenza-like symptoms, peripheral oedema, pain.

Laboratory findings
In placebo-controlled monotherapy studies, the incidence was somewhat higher on olmesartan medoxomil compared with placebo for hypertriglyceridaemia (2.0% versus 1.1%) and for raised creatine phosphokinase (1.3% versus 0.7%).

Laboratory adverse events reported across all clinical trials with olmesartan medoxomil (including trials without a placebo control), irrespective of causality or incidence relative to placebo, included:

Metabolic and nutritional disorders:
Common: Increased creatine phosphokinase, hypertriglyceridaemia, hyperuricaemia.
Rare: Hyperkalaemia

Liver and biliary disorders:
Common: Liver enzyme elevations.

Hydrochlorothiazide
Hydrochlorothiazide may cause or exacerbate volume depletion, which may lead to electrolyte imbalance (see section 4.4 - **Special warnings and special precautions for use**).

Adverse events reported with the use of hydrochlorothiazide alone include:

Gastrointestinal system disorders
Anorexia, loss of appetite, gastric irritation, diarrhoea, constipation, sialadenitis, pancreatitis

Hepatobiliary disorders
Jaundice (intrahepatic cholestatic jaundice)

Eye disorders
Xanthopsia, transient blurred vision

Blood and lymphatic system disorders
Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression

Skin and subcutaneous tissue disorders
Photosensitivity reactions, rash, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus, erythematosus, urticaria, necrotising angiitis (vasculitis, cutaneous vasculitis), anaphylactic reactions, toxic epidermal necrolysis

General disorders
Fever

Respiratory system disorders
Respiratory distress (including pneumonitis and pulmonary oedema)

Renal and urinary disorders
Renal dysfunction, interstitial nephritis

Musculoskeletal disorders
Muscle spasm, weakness

Nervous system disorders
Restlessness, light-headedness, vertigo, paresthesia

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer, especially squamous cell carcinoma in white patients with increasing cumulative doses.

Vascular disorders
Postural hypotension

Cardiac disorders
Cardiac arrhythmias

Psychiatric disorders
Sleep disturbances, depression

Laboratory findings
Hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), increases in cholesterol and triglycerides

4.9 Overdose
No specific information is available on the effects or treatment of Olmetec Plus overdosage. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends upon the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdosage. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

The most likely manifestations of olmesartan overdosage are expected to be hypotension and tachycardia; bradycardia might also occur. Overdosage with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdosage are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac

arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic drugs.

No information is available regarding the dialysability of olmesartan or hydrochlorothiazide.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Angiotensin II antagonists and diuretics, ATC code C09D A.

Olmetec Plus is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. Once daily dosing with Olmetec Plus provides an effective and smooth reduction in blood pressure over the 24-hour dose interval.

Olmesartan medoxomil is a potent, orally active, selective angiotensin II receptor (type AT1) antagonist. Angiotensin II is the primary vasoactive hormone of the renin angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension. The effects of angiotensin II include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by blocking its binding to the AT1 receptor in tissues including vascular smooth muscle and the adrenal gland. The action of olmesartan is independent of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT1) receptors by olmesartan results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.

In hypertension, olmesartan medoxomil causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after abrupt cessation of therapy.

Once daily dosing with olmesartan medoxomil provides an effective and smooth reduction in blood pressure over the 24-hour dose interval. Once daily dosing produced similar decreases in blood pressure as twice daily dosing at the same total daily dose.

With continuous treatment, maximum reductions in blood pressure are achieved by 8 weeks after the initiation of therapy, although a substantial proportion of the blood pressure lowering effect is observed after 2 weeks of treatment.

The effect of olmesartan medoxomil on mortality and morbidity is not yet known.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of

electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, and therefore, co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics. With hydrochlorothiazide, onset of diuresis occurs at about 2 hours and peak effect occurs at about 4 hours post dose, whilst the action persists for approximately 6-12 hours.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

The combination of olmesartan medoxomil and hydrochlorothiazide produces additive reductions in blood pressure which generally increase with the dose of each component. In pooled placebo-controlled studies, administration of the 20/12.5 mg, 40/12.5 mg and 40/25 mg combinations of olmesartan medoxomil/hydrochlorothiazide resulted in mean placebo-subtracted systolic/diastolic blood pressure reductions at trough ranging from 12/7 to 16/9 mm Hg. Age and gender had no clinically relevant effect on response to treatment with olmesartan medoxomil/hydrochlorothiazide combination therapy.

Administration of 12.5 mg and 25 mg hydrochlorothiazide in patients insufficiently controlled by olmesartan medoxomil 20 mg monotherapy gave additional reductions in 24-hour systolic/diastolic blood pressures measured by ambulatory blood pressure monitoring of 7/5 mm Hg and 12/7 mm Hg, respectively, compared with olmesartan medoxomil monotherapy baseline. The additional mean systolic/diastolic blood pressure reductions at trough compared with baseline, measured conventionally, were 11/10 mm Hg and 16/11 mm Hg, respectively. The addition of 12.5 mg hydrochlorothiazide in patients not achieving target blood pressure (≤130/85 mm Hg) on olmesartan medoxomil 40 mg decreased systolic/diastolic blood pressure by an additional 13/6 mm Hg, and titration of the hydrochlorothiazide dose to 25 mg in non-achievers at the lower add-on dose resulted in a further blood pressure decrease of 9/5 mm Hg. Conversely, addition of olmesartan medoxomil 10 - 20 mg in patients with moderate to severe hypertension insufficiently controlled by hydrochlorothiazide 25 mg monotherapy provided mean systolic/diastolic blood pressure reductions at trough of 21/18 mm Hg compared with hydrochlorothiazide monotherapy baseline.

The effectiveness of olmesartan medoxomil/hydrochlorothiazide combination therapy was maintained over long-term (one-year) treatment. Withdrawal of olmesartan medoxomil therapy, with or without concomitant hydrochlorothiazide therapy, did not result in rebound hypertension.

The effects of fixed-dose combination of olmesartan medoxomil/hydrochlorothiazide on mortality and cardiovascular morbidity are currently unknown.

5.2 Pharmacokinetic properties
Concomitant administration of olmesartan medoxomil and hydrochlorothiazide had no clinically relevant effects on the pharmacokinetics of either component in healthy subjects.

Absorption and distribution
Olmesartan medoxomil:
Olmesartan medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, olmesartan, by esterases in the gut mucosa and in portal blood during absorption from the gastrointestinal tract. No intact olmesartan medoxomil or intact side chain medoxomil moiety have been detected in plasma or excreta. The mean absolute bioavailability of olmesartan from a tablet formulation was 25.6%.

The mean peak plasma concentration (C_{max}) of olmesartan is reached within about 2 hours after oral dosing with olmesartan medoxomil, and olmesartan plasma concentrations increase approximately linearly with increasing single oral doses up to about 80 mg.

Food had minimal effect on the bioavailability of olmesartan and therefore, olmesartan medoxomil may be administered with or without food.

No clinically relevant gender-related differences in the pharmacokinetics of olmesartan have been observed.

Olmesartan is highly bound to plasma protein (99.7%), but the potential for clinically significant protein binding displacement interactions between olmesartan and other highly bound co-administered drugs is low (as confirmed by the lack of a clinically significant interaction between olmesartan medoxomil and warfarin). The binding of olmesartan to blood cells is negligible. The mean volume of distribution after intravenous dosing is low (16 – 29 L).

Hydrochlorothiazide:
Following oral administration of olmesartan medoxomil and hydrochlorothiazide in combination, the median time to peak concentrations of hydrochlorothiazide was 1.5 to 2 hours after dosing. Hydrochlorothiazide is 68% protein bound in the plasma and its apparent volume of distribution is 0.83 – 1.14 L/kg.

Metabolism and elimination
Olmesartan medoxomil:
Total plasma clearance of olmesartan was typically 1.3 L/h (CV, 19%) and was relatively slow compared to hepatic blood flow (ca 90 L/h). Following a single oral dose of ^{14}C-labelled olmesartan medoxomil, 10% - 16% of the administered radioactivity was excreted in the urine (the vast majority within 24 hours of dose administration) and the remainder of the

recovered radioactivity was excreted in the faeces. Based on the systemic availability of 25.6%, it can be calculated that absorbed olmesartan is cleared by both renal excretion (ca 40%) and hepato-biliary excretion (ca 60%). All recovered radioactivity was identified as olmesartan. No other significant metabolite was detected. Enterohepatic recycling of olmesartan is minimal. Since a large proportion of olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated (see section 4.3 - **Contraindications**).

The terminal elimination half-life of olmesartan varied between 10 and 15 hours after multiple oral dosing. Steady state was reached after the first few doses and no further accumulation was evident after 14 days of repeated dosing. Renal clearance was approximately 0.5 – 0.7 L/h and was independent of dose.

Hydrochlorothiazide:
Hydrochlorothiazide is not metabolised in man and is excreted almost entirely as unchanged drug in urine. About 60% of the oral dose is eliminated as unchanged drug within 48 hours. Renal clearance is about 250 – 300 mL/min. The terminal elimination half-life of hydrochlorothiazide is 10 – 15 hours.

Pharmacokinetics in special populations
Elderly:
In hypertensive patients, the olmesartan AUC at steady state was increased by ca 35% in elderly patients (65 - 75 years old) and by ca 44% in very elderly patients (≥75 years old) compared with the younger age group (see section 4.2 - **Posology and method of administration**).

Renal impairment:
In renally impaired patients, the olmesartan AUC at steady state increased by 62%, 82% and 179% in patients with mild, moderate and severe renal impairment, respectively, compared to healthy controls (see sections 4.2- **Posology and method of administration** and 4.4 - **Special warnings and special precautions for use**).

Hepatic impairment:
After single oral administration, olmesartan AUC values were 6% and 65% higher in mildly and moderately hepatically impaired patients, respectively, than in their corresponding matched healthy controls. The unbound fraction of olmesartan at 2 hours post-dose in healthy subjects, in patients with mild hepatic impairment and in patients with moderate hepatic impairment was 0.26%, 0.34% and 0.41%, respectively. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment (see sections 4.2 - **Posology and method of administration** and 4.4 - **Special warnings and special precautions for use**).

5.3 Preclinical safety data
The toxic potential of Olmetec Plus was evaluated in repeated dose oral toxicity studies with olmesartan medoxomil/hydrochlorothiazide combinations for up to six months in rats and

dogs. Most observations were due to the pharmacological activity of the combination and there were no findings that would preclude administration to humans at the therapeutic dosage level.

There was no evidence of relevant genotoxic activity under conditions of clinical use. Olmesartan medoxomil/hydrochlorothiazide in a ratio of 20:12.5 was negative in the bacterial reverse mutation test up to the maximum recommended plate concentration for the standard assays. Olmesartan medoxomil and hydrochlorothiazide were tested individually and in combination ratios of 40:12.5, 20:12.5 and 10:12.5, for clastogenic activity in the *in vitro* Chinese hamster lung chromosomal aberration assay. As expected, a positive response was seen for each component and combination ratio. However, no synergism in clastogenic activity was detected between olmesartan medoxomil and hydrochlorothiazide at any combination ratio. Olmesartan medoxomil/hydrochlorothiazide in a ratio of 20:12.5, administered orally, tested negative in the *in vivo* mouse bone marrow erythrocyte micronucleus assay at administered doses of up to 1935/1209 mg/kg.

The carcinogenic potential of a combination of olmesartan medoxomil and hydrochlorothiazide was not investigated as there was no evidence of relevant carcinogenic effects for the two individual components under conditions of clinical use.

There was no evidence of teratogenicity in mice or rats treated with olmesartan medoxomil/hydrochlorothiazide combinations. As expected from this class of drug, foetal toxicity was observed in rats, as evidenced by significantly reduced foetal body weights, when treated with olmesartan medoxomil/hydrochlorothiazide combinations during gestation (see sections 4.3 - **Contraindications** and 4.6 - **Pregnancy and lactation**).

5.4 Clinical trials

The Randomised Olmesartan And Diabetes Microalbuminuria Prevention (ROADMAP) clinical study included 4447 patients with type 2 diabetes, normoalbuminuria and at least one additional cardiovascular risk factor. Patients were randomized to olmesartan 40 mg daily or placebo. The trial met its primary endpoint, delayed onset of microalbuminuria. For the secondary endpoints, which the study was not designed to formally assess, cardiovascular events occurred in 96 patients (4.3%) with olmesartan and in 94 patients (4.2%) with placebo. The incidence of cardiovascular mortality was higher with olmesartan compared to placebo treatment (15 patients [0.67%] vs. 3 patients [0.14%] [HR=4.94, 95% CI=1.43-17.06]), but the risk of non-fatal myocardial infarction was lower with olmesartan (HR 0.64, 95% CI 0.35, 1.18).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Lactose monohydrate
Hydroxypropylcellulose

Magnesium stearate

Tablet coat
Talc
Hypromellose
Titanium dioxide (E 171)
Iron oxide yellow (E 172)
Iron oxide red (E 172)

6.2 Incompatibilities
Not applicable.

6.3 Special precautions for storage
Store below 30°C.

6.4 Instructions for use and handling, and disposal
No special requirements.

Prescription Only

HARUS DENGAN RESEP DOKTER

SUPPLY
OLMETEC PLUS 20/12.5 mg Film-Coated Tablet; Box of 30 tablets; Reg. No.: DKI1890701817A1
OLMETEC PLUS 40/12.5 mg Film-Coated Tablet; Box of 30 tablets; Reg. No.: DKI1890701817B1

Manufactured by:
Daiichi Sankyo Europe GmbH,
Germany

Packed and released by:
Pfizer Manufacturing Deutschland GmbH,
Freiburg, Germany

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia